Hypertension Curriculum Review

Donald G. Vidt, MD, Section Editor

Cardioprotection: The Role of β-Blocker Therapy

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Randomized controlled clinical trials document that β blockers reduce cardiovascular morbidity and mortality, particularly sudden death, in patients with hypertension, heart failure, and post-myocardial infarction. The benefits of β blockers extend across the boundaries of age, gender, and ethnicity, and include diabetic patients with heart failure and/or previous myocardial infarction. Unfortunately, β blockers remain underutilized in many high-risk patients who would likely benefit from their use. This paper reviews the protective role of β blockade in the primary and secondary prevention of cardiovascular events and examines some of the potential barriers to appropriate β blocker use in patients with compelling indications. (J Clin Hypertens. 2005;7:409–416) ©2005 Le Jacq Ltd.

Cardiovascular disease (CVD) is the leading cause of mortality among men and women in the United States, accounting for approximately 40% of deaths in 2001. Dyslipidemia, hypertension, and diabetes are major risk factors for atherosclerosis and CVD. Appropriate management of these risk factors reduces the incidence of coronary artery disease (CAD) and left ventricular (LV) hypertrophy and the progression to myocardial infarction (MI), heart failure (HF), and death (Figure 1). A series of evidence-based trials has established effective interventions for patients at virtually every step in the cardiovascular (CV) continuum, from asymptomatic high-risk individuals to patients with advanced HF. It is important to interrupt the chain of events as early as possible to help prevent or slow the progression to overt CVD and death.

The Framingham Heart Study showed a strong association between hypertension and CV and renal disease outcomes, including CAD, MI, HF, stroke, and kidney failure. Chronic hypertension can lead to HF by two pathways: cardiac hypertrophy and cardiac ischemia, which often occur together. While the development of HF reflects the complex interplay of multiple pathophysiologic processes, hypertension precedes HF in at least 90% of all cases. Lifetime risk for HF is doubled in patients with blood pressure (BP) ≥160/100 mm Hg vs. <140/90 mm Hg. The relationship between high BP and HF is continuous and independent of other risk factors. Antihypertensive treatment reduces the incidence of HF by approximately 50%.

Beta blockers reduce total deaths and CV morbidity and mortality in men and women post-MI and/or with HF. The effects of β blockers for primary prevention of events in uncomplicated hypertensive patients are more variable and may reflect demographic differences in study subjects or variations in the pharmacologic effects of the specific β blocker studied. The trial results are consistent in showing that β blockers, particularly those without intrinsic sympathomimetic activity (ISA), reduce sudden cardiac deaths by 30% or more in

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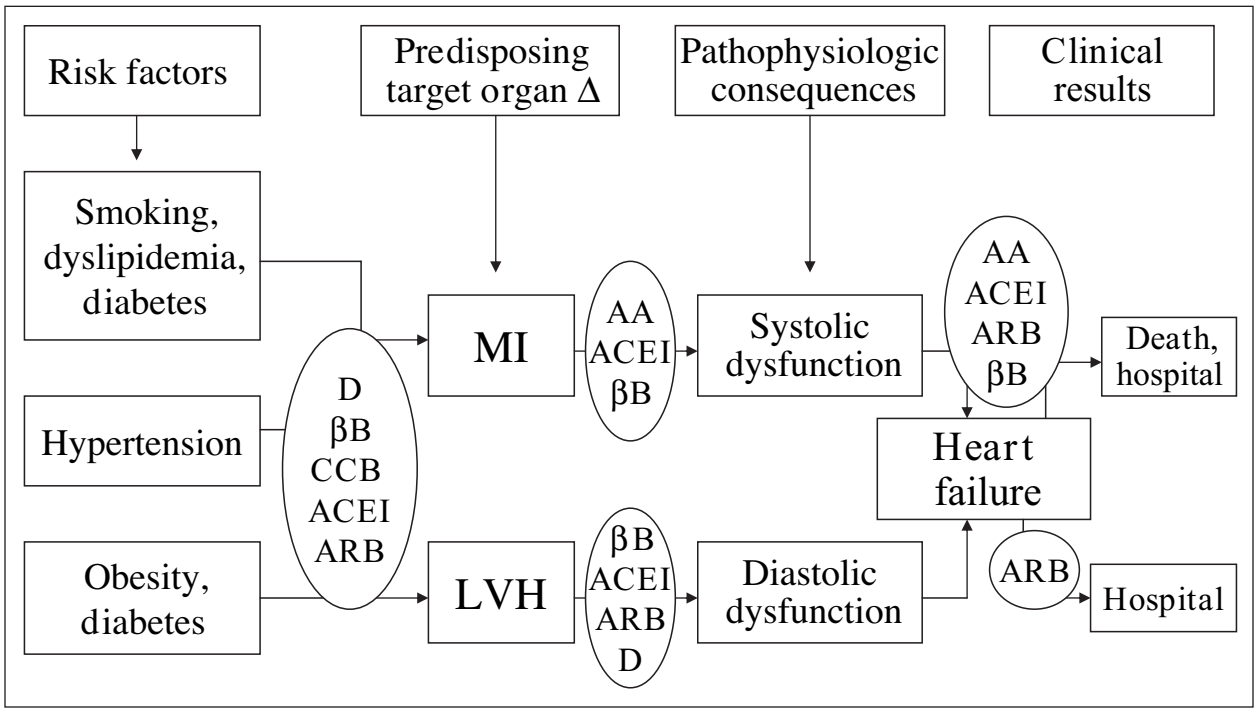

Figure 1. The heart failure continuum, from risk factors for predisposing target organ changes (Δs) (myocardial infarction [MI] and left ventricular hypertrophy [LVH]) and pathophysiologic consequences (systolic and diastolic dysfunction) to clinical outcomes (heart failure, hospitalization, and death, which is often sudden). There are several opportunities along the continuum for evidence-based interventions, as shown, including aldosterone antagonists (AAs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β blockers (βBs), calcium channel blockers (CCBs), and diuretics (Ds). Adapted from Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. Arch Intern Med. *1996;156(16):1789–1796.*

select groups of hypertension, HF, and post-MI patients. Despite proven benefit, β blockers are underutilized in many high-risk patients.

The purposes of this paper are: 1) to review the role of heart rate (HR) and the sympathetic nervous system (SNS) in the pathophysiology of hypertension, LV hypertrophy, HF, and atherosclerosis; 2) to examine the role for β blockade in the primary and secondary prevention of cardiac events; 3) to recommend appropriate use of β blockers in patients who are likely to derive significant clinical benefits from such treatment; and 4) to discuss potential barriers to appropriate β-blocker use.

ROLE OF THE SNS IN HYPERTENSION AND CVD

The SNS mediates actions in the heart, blood vessels, and kidneys—primarily through the neural release of norepinephrine. Norepinephrine stimulates β_1-adrenergic receptors in the heart to raise HR and increase calcium influx and uptake, which enhances myocardial contractility. Chronically elevated levels of norepinephrine affect individual myocytes and may trigger programmed cell death, or apoptosis. Sympathetic nerve traffic to the kidney activates β-adrenergic receptors that augment renin release, which, in turn, raises angiotensin and aldosterone concentrations implicated in LV hypertrophy and HF.

Chronic SNS stimulation is associated with HF via a number of responses (Figure 2), including tachycardia, activation of the renin–angiotensin–aldosterone system, decreased cardiac blood flow, and myocardial remodeling. Activation of the SNS may provoke arrhythmias by increasing HR and the automaticity of cardiac cells and by promoting hypokalemia. The degree of SNS activation, as measured by plasma norepinephrine, was independently associated with increased risk of death in the Vasodilator Heart Failure Trial II (V-HeFT II).

The Link Between HR and Heart Disease

Faster HRs are associated with greater risk of sudden death and poorer outcomes in patients with HF and coronary heart disease. Reduced HR variability in patients with CVD is also linked to more adverse outcomes, including sudden death. HR and HR variability are controlled by the autonomic nervous system—activation of the SNS increases HR and decreases variability, while activation of the parasympathetic branch decreases HR and enhances variability. Faster HRs may increase pulsatile stresses on the vascular system, particularly at branch points,

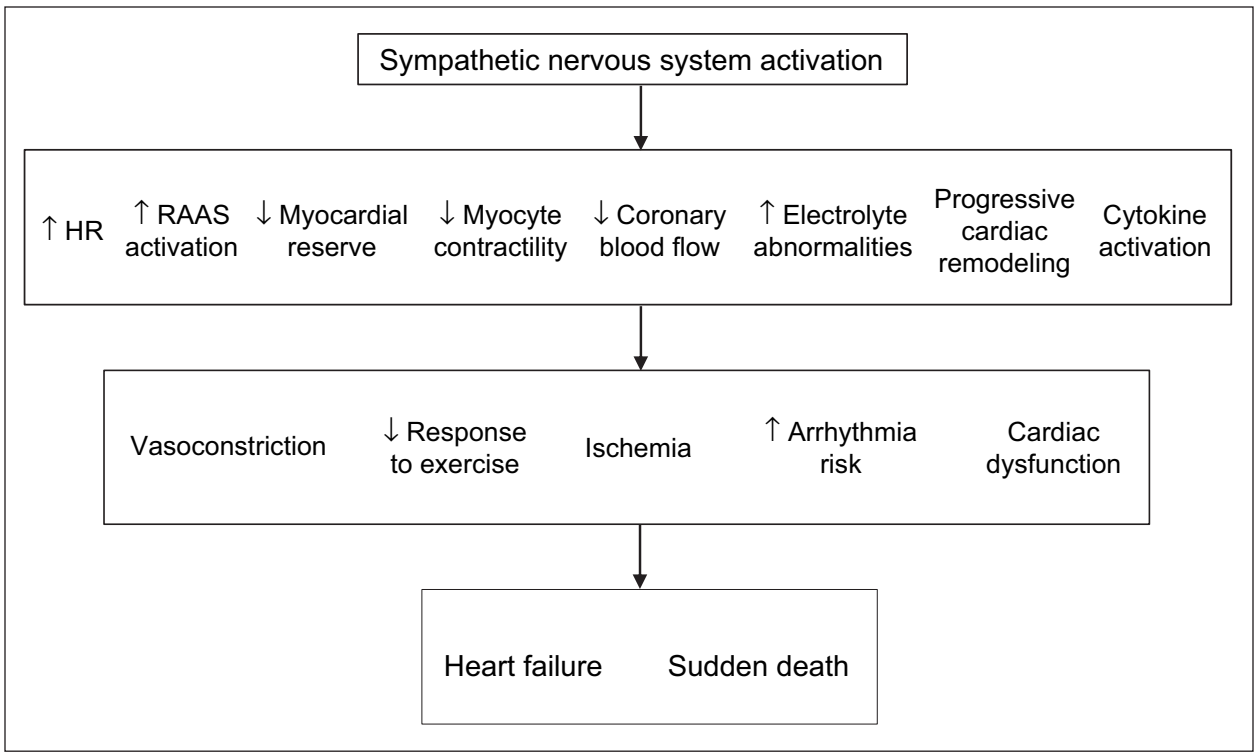

Figure 2. Chronic sympathetic nervous system activation leads to multiple responses that contribute to heart failure and sudden death. HR=heart rate; RAAS=renin–angiotensin–aldosterone system; ↑=increased; ↓=decreased

and may augment atherosclerotic lesions, and perhaps plaque rupture. Faster HRs also increase the risk of cardiac ischemia by reducing the amount of diastolic time—when LV perfusion occurs.

Among hypertensive patients 35–74 years of age in the Framingham Study, 36-year follow-up data showed that higher HRs were associated with a roughly 2.2-fold greater risk for all-cause mortality and 1.7-fold higher CV mortality. Men with HRs ≥88 bpm were at a roughly 6-fold greater risk of sudden death compared with men who had HRs <65 bpm. In another study of patients admitted with an acute MI, the greater the maximal HR in the intensive care unit, the higher the 1-year mortality. Studies of β-blocker therapy post-MI show that the decrease in mortality correlates strongly with the reduction in HR (Figure 3).

In the Assessment of Treatment With Lisinopril and Survival (ATLAS) study, HF patients with higher HRs were at increased risk for all-cause mortality, CV death, sudden death, and HF death. Beta-blocker use in ATLAS was associated with a reduction in sudden death. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) showed that HR reduction at 2 months was associated with improved survival and reduced hospital admissions. Lower HRs were also associated with decreased morbidity and mortality in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF).

BETA$_1$-ADRENERGIC BLOCKING AGENTS: CLINICAL CONSIDERATIONS

Mechanism of Action and Clinical Pharmacology

Beta-adrenergic receptor antagonists lessen the deleterious effects of norepinephrine on the heart and kidney that are mediated by the β_1 receptor. Some β blockers, e.g., propranolol and nadolol, block both β_1 and β_2 receptors, while other β blockers, e.g., atenolol, bisoprolol, and metoprolol, block β_1 receptors preferentially. Because cardiac tissue contains predominantly β_1 receptors, β_1 blockers are considered cardioselective, and they tend to have fewer adverse side effects associated with β_2 blockade in the lung and peripheral tissues. Selectivity is dose-dependent; at high doses, selective β blockers can induce clinically significant antagonism of the β_2 receptor. Some β blockers, e.g., carvedilol and labetalol, block β_1 and β_2 receptors as well as α_1 receptors. Other β blockers have ISA, e.g., acebutolol and pindolol, which leads to weak stimulation of β-adrenergic receptors while blocking the effects of catecholamines. Beta blockers with ISA lower HR less than β blockers without ISA and provide less cardioprotection; they should generally be avoided in HF and post-MI patients.

Attributes of β blockers make them particularly useful in treating hypertension and HF. Beta blockers have antihypertensive, antiarrhythmic, and anti-ischemic effects, and there is some evidence for antiatherogenic effects. Beta blockers inhibit sympathetic outflow

Table. Summary of Recommendations for Use of β Blockers for Specific Clinical Conditions

Clinical Condition	Summary of Recommendations
Hypertension	Unless contraindicated, β blockers may be used as initial therapy or in combination with agents from other classes in the treatment of uncomplicated hypertension. Beta blockers are generally as effective at lowering blood pressure as other classes of antihypertensive agents, although their efficacy may be less in the elderly and patients of African descent, compared with younger and Caucasian patients. Beta blockers are cardioprotective in hypertensive patients at risk for CAD, HF, or SCD.
Heart failure	Unless contraindicated, β blockers are an essential part of the drug regimen for HF patients, based upon their proven ability to improve symptoms and decrease death and hospitalizations. In NYHA classes II–IV, HF is a strong indication for use of β blockers, particularly in combination with ACE inhibitors and/or diuretics. Beta blockers significantly reduce the risk of sudden death by up to 45% in this population.
CAD and high risk for CAD	Beta blockers are recommended for primary prevention of CAD as well as for patients with symptomatic or asymptomatic CAD.
Acute MI, post-MI, and angina	Prevention of coronary events in patients with angina, during acute MI, and in post-MI patients; includes the use of aspirin, ACE inhibitors, and β blockers. Beta blockers should be used in the treatment of stable angina and titrated to achieve a target HR of approximately 55–60 bpm. In patients with more severe angina, the target HR may be <50 bpm provided symptoms associated with bradycardia and heart block do not develop. Beta-blocker therapy should not be abruptly discontinued in patients with ischemic heart disease; rather, the dosage should be gradually reduced over 1–2 weeks.
Diabetes	Beta blockers may be selected as initial therapy or in combination with other agents in the treatment of hypertension in diabetic patients. Beta blockers reduce morbidity and mortality in diabetics with HF and post-MI.
SCD	Beta blockers, alone and in combination with other interventions, have demonstrated substantial benefits in reducing the incidence of SCD and thus should be considered for use in patients who have risk factors for SCD. This group may include asymptomatic patients with multiple risk factors for CAD and patients with previous MI, coronary ischemia, impaired left ventricular function, and previous life-threatening ventricular arrhythmias. Other risk factors for SCD include excessive alcohol consumption, increased HR/decreased HR variability, ECG abnormalities, genetic abnormalities, and medications causing prolonged QT interval.
Elderly hypertension	Beta blockers have demonstrated significant reductions in morbidity and mortality in the elderly. Older age should not be viewed as a contraindication to their use, especially when a compelling indication for their use exists.
Perioperative management	The perioperative use of β blockers has shown benefits in patients with or at risk for CAD, including a reduction in the incidence of myocardial complications and an improvement in overall survival.

CAD=coronary artery disease; HF=heart failure; SCD=sudden cardiac death; NYHA=New York Heart Association; ACE=angiotensin-converting enzyme; MI=myocardial infarction; HR=heart rate; ECG=electrocardiographic

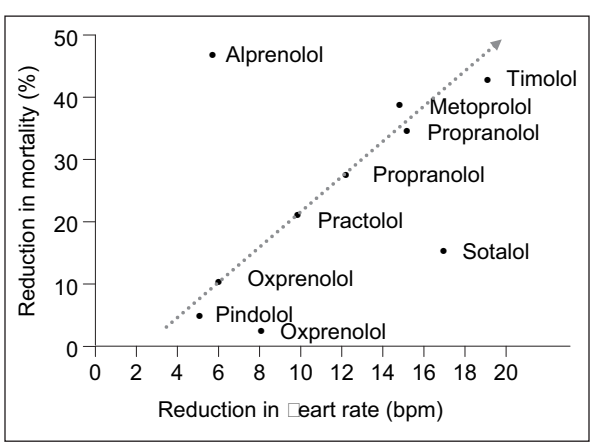

Figure 3. Relationship between reduction in heart rate (difference between treatment groups) and percentage reduction in mortality in post-myocardial infarction patients in large, prospective, double-blind β-blocker trials. Adapted from Eur Heart J. *1987;8(suppl L):115–122.*

centrally, slow HR, decrease cardiac contractility, and reduce renin–angiotensin–aldosterone system activity by inhibiting renin release. Compared with other antihypertensives, β blockers have the greatest combined effect on reducing BP, HR, and myocardial contractility, which are three major determinants of myocardial O_2 consumption. Beta blockers reduce tachyarrhythmias associated with sudden death. By lowering HR and contractility, β blockers reduce the pulsatile forces of blood flow within the arterial system, which may decrease the risk of plaque rupture.

Factors Contributing to Underutilization of β Blockers in High-Risk Patients

As newer classes of antihypertensive agents, including calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers have become available, β blockers have become less prominent in the treatment

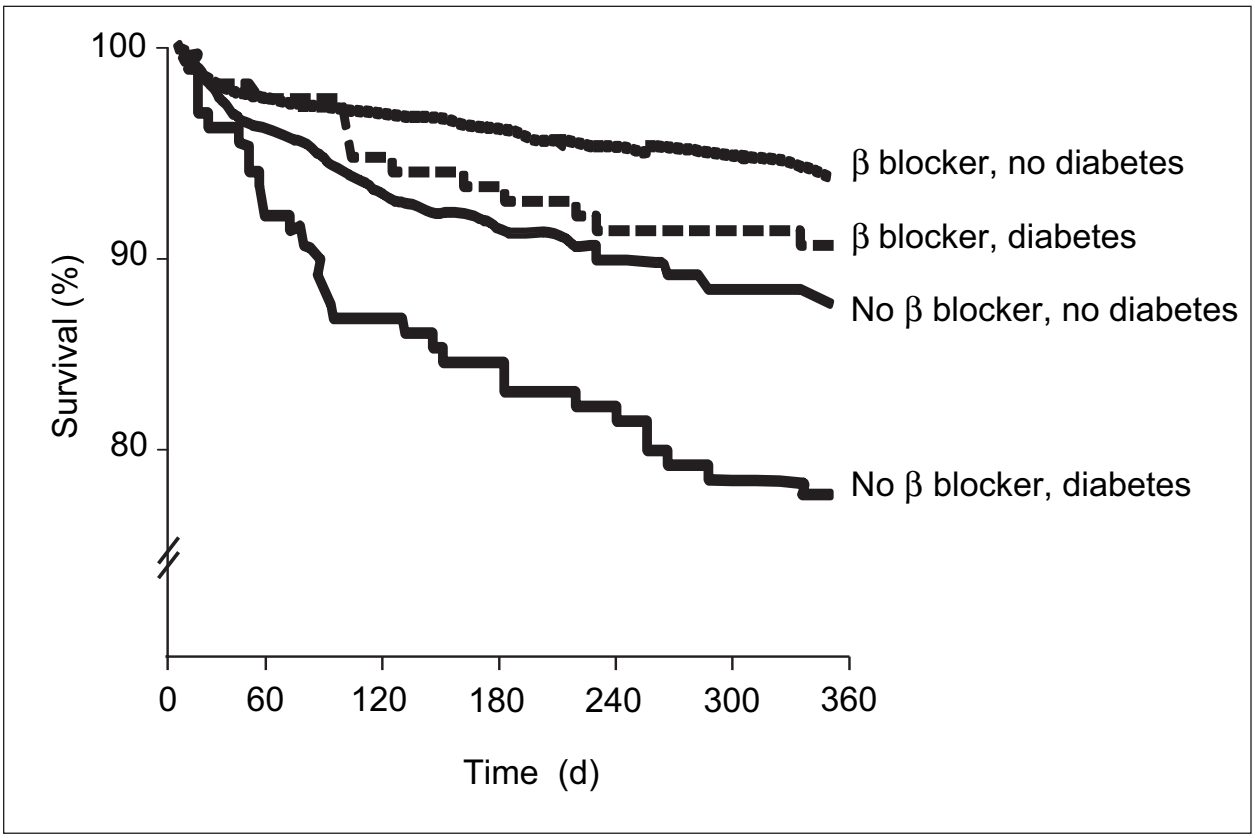

Figure 4. Data from a large multicenter cohort (N=2024) examined 1-year survival following acute myocardial infarction by β blocker and diabetic status. Survival from the time of hospital discharge to 1 year was significantly better for patients both with and without diabetes taking β blockers (p<0.001 for both comparisons). One-year mortality following discharge was 17% vs. 10% for diabetic patients compared with nondiabetic patients; 10% vs. 23% for diabetic patients taking β blockers compared with diabetic patients not taking β blockers; and 7% vs. 13% for nondiabetic patients taking β blockers compared with nondiabetic patients not taking β blockers. Adapted from Eur Heart J. *1990;11:43–50.*

of hypertension and HF. Lower β-blocker usage may be partially attributable to the greater range of options and the lesser familiarity by clinicians with evidence from earlier large-scale β-blocker trials.

Underprescribing and inadequate dosing of β blockers may also reflect physicians' concerns about side effects; however, the differences in adverse-effect profiles between newer and older agents are often small in randomized double-blind trials. In the Veterans Affairs Cooperative Study of hypertension, discontinuation rates for β blockers were comparable to placebo and ACE inhibitors. In placebo-controlled trials with more than 35,000 subjects, β_1 blockers were not associated with a significant increase in depressive symptoms, and fatigue and sexual dysfunction were only modestly increased.

Concerns about β-blocker–induced weight gain and adverse metabolic effects may also deter physicians from prescribing these agents. Placebo-controlled trials suggest that β blockers are associated with an average 1.2-kg weight gain during the first few months, but no further weight gain relative to placebo thereafter. Beta blockers can adversely affect glucose and lipid metabolism. These metabolic effects are generally minimal or nonexistent with combined α–β blockers and β blockers with ISA, relatively small with cardioselective β_1 blockers, and greatest with nonselective β blockers. The long-term implications of pharmacologically induced metabolic changes have not been proven in randomized clinical trials. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that thiazide diuretics were superior to α_1 antagonists in reducing CV events, despite the more favorable effects of the latter on glucose and lipid metabolism.

Beta blockers are associated with a modestly increased incidence of type 2 diabetes mellitus. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, the incidence of diabetes was 25% lower with losartan than with atenolol, although the absolute difference in the rates was 2%, i.e., 6% vs. 8% per 1000 patient-years of follow-up. Nevertheless, β blockers remain important for patients with the metabolic syndrome or diabetes who have compelling indications, including HF, previous MI, or other risk factors for sudden death.

Beta blockers, by inhibiting β_2-adrenergic receptors, can exacerbate reactive airway disease. Patients with chronic obstructive pulmonary disease often do not have a significant bronchospastic component. Selective β_1 blockers, beginning at low doses and titrating upward as tolerated, have cardioprotective effects in post-MI and HF patients with mild-to-moderate chronic obstructive pulmonary disease. Thus, chronic obstructive pulmonary disease should not preclude β blockers when compelling indications exist. As a practical precaution, some physicians assess the bronchodilator response to β agonists in pulmonary function testing before initiating β blockers.

EVIDENCE-BASED CLINICAL RECOMMENDATIONS FOR β-BLOCKER USE

General Considerations

Beta blockers have important clinical benefits and are approved for use in hypertension, HF, mitral valve prolapse, silent myocardial ischemia, glaucoma, and thyrotoxicosis. Migraine headaches and essential tremor often improve with nonselective β blockers. Perioperative use of β blockers reduces complications in patients with hypertension and those at risk for cardiac ischemia.

Recommendations for the use of β blockers are summarized in the Table. In general, β blockers should be initiated at the lowest recommended starting dose and titrated to the dose proven beneficial in clinical trials. Patients should be monitored during titration for adverse effects, such as significant bradycardia or orthostatic hypotension, that serve as limits to further up-titration. Of note, HF patients who experience HR control at lower doses appear to derive benefits similar to those in patients given the higher target dose. Most hypertensive patients require more than one drug to control BP, and β blockers are safe and effective in combination with other major antihypertensive drug classes.

There are relatively few contraindications to β-blocker use. Beta blockers should not be administered to patients with second- or third-degree heart block, and they are generally contraindicated in asthmatics. Given the potential for additive reductions of HR and cardiac contractility, the combination of a β blocker and a nondihydropyridine CCB, e.g., verapamil or diltiazem, is not generally recommended.

Hypertension

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends thiazide diuretics as initial therapy for patients with uncomplicated hypertension, but very few hypertensive cases are uncomplicated. Based on data from numerous large-scale trials, JNC 7 notes compelling indications for several classes of antihypertensive agents, including the use of β blockers in diabetic, HF, or post-MI hypertensive patients, as well as for primary prevention in patients at high risk for CAD. Beta blockers are similar in antihypertensive efficacy to other currently available classes of agents as monotherapy. Clinical trials suggest that β-blocker monotherapy is relatively more effective at lowering BP in younger patients, men, and Caucasians than in older patients, women, and African Americans.

Heart Failure

The goals of treatment for chronic HF are to improve quality of life by relieving symptoms and to decrease morbidity and mortality. Data from numerous studies strongly support the addition of β-blocker therapy to the treatment regimen of all clinically stable patients with New York Heart Association (NYHA) class II–IV HF, due to significant reductions in overall mortality and in hospitalizations for worsening HF.

The CIBIS-II, MERIT-HF, and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) studies all demonstrated virtually identical morbidity and mortality benefits in HF patients when β blockers were added to background therapy with ACE inhibitors, diuretics, and digoxin. Beta blockers reduced mortality in pooled data of patients with severe HF (NYHA class III–IV) included in these three trials. Meta-analyses support the use of β blockers in men and women, diabetic and nondiabetic, black and white, and younger and older patients with HF. Data from 22 randomized clinical trials with more than 10,000 HF patients suggest that the first year of β-blocker therapy would lead to 3.8 fewer deaths and four fewer hospitalizations per 100 patients treated. Over 7 months, treating 38, 24, or 15 patients with a β blocker would prevent one death, one HF hospitalization, and one combined outcome of death or hospitalization for HF, respectively.

Coronary Artery Disease

Beta blockers are recommended for primary prevention of ischemic heart disease as well as for secondary prevention of CV morbidity and mortality in high-risk patients, as summarized in the JNC 7 report. Beta blockers appear to have favorable effects on vascular remodeling during the early stages of atherosclerosis. In a 3-year trial, extended-release metoprolol succinate reduced carotid intima-media thickening in 793 men and women with no symptoms of CAD and asymptomatic right carotid artery

plaque. Beta blockade slowed progression of intima-media thickening at the bifurcation, but not in the common carotid artery, whereas treatment with fluvastatin slowed progression in the common carotid, but not in the bifurcation, suggesting different effects of statins and β blockers at different portions of the arterial tree. While the carotid intima-media thickening data are provocative, the effects of β blockers on coronary atherosclerosis are not known.

The use of aspirin and β blockers is generally recommended for all patients with angina, during acute MI, and post-MI. American College of Cardiology/American Heart Association guidelines recommend β blockers for the treatment of stable angina to lower HR and reduce myocardial O_2 consumption. The target resting HR should be 55–60 bpm in these patients, while the increase in HR during exercise should not exceed 75% of the HR response associated with the onset of ischemia. In patients with more severe angina, resting HR can be reduced to <50 bpm provided that symptomatic bradycardia and heart block do not occur. Administration of IV β blockers during acute MI, continued orally thereafter, provides a survival benefit within 90 days post-MI that persists for at least 6 years. Beta-blocker therapy should not be abruptly discontinued in patients with CAD, as this may exacerbate angina and possibly lead to MI. If it is necessary to discontinue therapy, the dosage should be tapered over 1–2 weeks, and the patient monitored carefully.

Sudden Cardiac Death

Approximately 50% of men and 63% of women with sudden cardiac death had no previous symptoms. Preventing sudden death requires identification of the large pool of patients at risk, including those with previous MI, LV hypertrophy and/or dysfunction, and known CAD as well as major risk factors for CAD, e.g., dyslipidemia, smoking, and diabetes. Other risk factors for sudden death include excessive alcohol consumption, increased HR/decreased HR variability, electrocardiographic abnormalities, genetic abnormalities, and medications that prolong the QT interval.

Beta blockers reduce sudden cardiac death by 30%–50% in patients with hypertension, HF, and CAD. The mechanisms may include reducing basal HR and intermittent episodes of tachycardia, direct antiarrhythmic properties, decreasing myocardial O_2 consumption and ischemia, lowering cardiac sympathetic tone, and augmenting cardiac vagal tone. Sudden death is the most common cause of death in patients with HF. Beta blockers reduce this risk by up to 45%, which is greater than any other class of antihypertensive or antiarrhythmic agents.

Special Populations

Despite proven benefits, β blockers are underutilized in African Americans, diabetic patients, and elderly patients with compelling indications.

African Americans. Clinical trials demonstrate that benefits with carvedilol and extended-release metoprolol succinate are similar among black and white patients with NYHA class II–IV HF. The Hypertension in African Americans Working Group recommends antihypertensive therapy with β blockers for African Americans using the same indications as for the general hypertensive population. Beta blockers, ACE inhibitors, and angiotensin receptor blockers tend to be less effective than diuretics or CCBs as monotherapy in black hypertensives. In combination with other agents, such as low-dose diuretics, β blockers provide similar BP-lowering efficacy in African Americans as in other populations. Most hypertensive African Americans require combination therapy to control BP, and β blockers are a logical component of the overall regimen for those with clinical indications.

Diabetics. Patients with diabetes are at increased risk for stroke, CV mortality, and CAD, including sudden cardiac death. The JNC 7 report lists diabetes as a compelling indication for β-blocker therapy. In the United Kingdom Prospective Diabetes Study (UKPDS), atenolol and captopril produced similar reductions in BP and microvascular and macrovascular outcomes over 9 years of follow-up. Since many hypertensive diabetics require multiple agents to achieve goal BP, β blockers should be considered in the antihypertensive regimen of diabetic patients, given the cardioprotective benefits. In post-MI patients, 1-year survival rates were substantially improved with β-blocker therapy among both diabetic and nondiabetic patients (Figure 4). Diabetics in MERIT-HF had similar reductions in overall death and hospitalizations for HF, compared with the total study population.

Concerns about adverse metabolic effects of β blockers should not preclude their use in diabetics with compelling indications. Most patients with type 2 diabetes do not have major or frequent hypoglycemic episodes which may be symptomatically masked by β blockers. Beta blockers can also delay recovery from hypoglycemia. Concerns about β-blocker–induced worsening of glucose and lipid metabolism in diabetic patients adversely affecting clinical outcomes have not been substantiated in clinical trials. In fact, the benefits of these agents for secondary prevention post-MI and in HF are at least as great in diabetics as nondiabetics.

Elderly Patients. Beta blockers are underprescribed in elderly (over 65 years of age) patients with compelling indications. In one meta-analysis, β-blocker therapy improved survival in post-MI patients aged under 70 years, 70–79 years, and 80 years or older. In another meta-analysis, β blockers improved survival in post-MI patients aged 75–84 years. The HF studies similarly indicate that the benefits of β blockers extend to older patients. Nevertheless, β blockers are generally not recommended as monotherapy for elderly hypertensives without compelling indications.

SUMMARY

High BP and faster HRs are associated with greater risk of CV mortality. Beta blockade reduces both of these hemodynamic factors by inhibiting the effects of an overactive SNS. Beta blockers are beneficial for a wide range of patients at risk for CV events, including patients with hypertension, diabetes, CAD, and HF. Beta blockers are effective antihypertensives when given as monotherapy and in combination with other classes of agents. Their utility has been demonstrated in numerous large-scale clinical trials for primary and secondary cardioprotection in hypertensive, HF, and post-MI patients. Beta blockers are especially effective in preventing sudden death. In various trials and meta-analyses, the cardioprotective benefits of β blockers extend to diabetic, elderly, and African-American patients. Although β blockers are associated with side effects in some individuals, randomized trials indicate that these agents are well tolerated by the majority of patients.

At the present time, β blockers remain underutilized in many high-risk patients who are likely to derive clinical benefit from their use. The majority of hypertensive patients require a combination of antihypertensive agents to attain BP control. Beta blockers should generally be included in the therapeutic regimens of high-risk groups, including diabetic, post-MI, and HF patients, as well as hypertensive patients with these comorobidities and/or elevated resting HRs. As indicated in Figure 1, ACE inhibitors and β blockers are evidence-based therapies for reducing the likelihood of progression at multiple points along the HF continuum—from risk factors to the anatomic and physiologic changes that lead to HF, hospitalization, and death. Early and appropriate utilization of these proven therapies is essential in reducing the substantial and growing health and economic burden related to HF.

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